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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,645	10/31/2000	Rainer Haas	100564-00035	6963

7590 11/07/2003

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,645	HAAS ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- Th MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53 and 57-103* is/are pending in the application.

4a) Of the above claim(s) *59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53, 57-58, 60-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 26, 2003 has been entered.

Applicants arguments and amendments set forth in the response of September 26, 2003 have been fully considered but are not persuasive to overcome all grounds of rejection. Receipt of the certified translation of priority document Germany 19823098.2 is acknowledged. All rejections not reiterated herein are hereby withdrawn. This action contains new grounds of rejection.

Election/Restrictions

2. It is noted that this application has been examined only to the extent that the claims are limited to the subject matter elected in the response of Paper No. 9. The elected subject matter is a method for detecting macrolide antibiotic resistance in Helicobacter, in particular, using probes comprising SEQ ID NO: 1. The non-elected subject matter which has not been examined includes claim 59, SEQ ID NO: 2-4 in claims 57-59, 78, 92 and 93, non-elected regions in claim 60 and non-elected microorganisms in claim 62.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53, 57-58 and 60-103 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detecting clarithromycin resistance in H. pylori wherein the methods comprise detecting the presence of a A to G or A to C mutation at position 2058 of the 23S rRNA of H. pylori as indicative of resistance of H. pylori to clarithromycin, does not reasonably provide enablement for methods of detecting antibiotic resistance in any microorganism by detecting any mutation in any peptidyltransferase center of 23S rRNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are very broadly drawn to methods for detecting macrolide antibiotic resistance in a microorganism wherein the methods comprise hybridizing a nucleic acid sample with a probe that is specific for the peptidyltransferase center of 23S rRNA in any microorganism which is associated with resistance to any antibiotic. The specification teaches (see, for example, page 6) six mutations in the 23S rRNA gene which result in resistance to the antibiotics chloramphenicol, clarithromycin, clinidamycin, erythromycin, linomycin and/or streptomycin in E.coli, P. acnes, M. pneumoniae, M. intracellular and/or H. pylori. As stated in *Vaek* (20 USPQ2d 1438), the "specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the

art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art". With respect to the present invention, one cannot readily anticipate what additional mutations in the 23S rRNA gene will result in resistance to antibiotics. The claims include an incredibly large genus of mutations which have not been adequately taught in the specification. The specification does not provide sufficient guidance as to how to identify additional mutations which confer resistance to antibiotics and which are specific for a microorganism. To identify additional mutations associated with antibiotic resistance in microorganisms would require extensive analysis of a large genus of 23S rRNA sequences from a representative number of microorganisms for the presence of a mutation associated with resistance to any one of a large number of possible antibiotics and then developing probes which are specific for that microorganism. Such experimentation is considered to be undue. As set forth on page 6 of the specification, the specified 23S rRNA mutations confer resistance to different antibiotics in different microorganisms. For example, the 2058 mutation in the 23S rRNA confers resistance to clarithromycin in H. pylori, but confers resistance to erythromycin in M. pneumoniae. Accordingly, there is no predictable means for

determining which mutations confer resistance to which antibiotics in a given microorganism. While the specification exemplifies methods which analyze the 23S rRNA for the presence of mutations at positions 2032, 2057, 2058, 2059, 2503 or 2611 in 5 microorganisms, only the mutation at position 2058 has been shown to confer antibiotic resistance H. pylori. The 2058 mutation has not been shown to confer resistance to any additional antibiotics in H. pylori and the 2058 mutation has not been shown to confer antibiotic resistance to any additional species of Helicobacter. The specification has not established that the stated mutations confer resistance to all antibiotics or that these mutations confer antibiotic resistance in all microorganisms. The ability to establish a correlation between the presence of a mutation and the occurrence of antibiotic resistance is highly unpredictable and can only be determined through extensive, random, trial and error experimentation. The claims require the use of probes that detect resistance to macrolide antibiotics. Such probes must hybridize to specific mutations in the 23S rRNA peptidyltransferase center wherein said mutations confer resistance to one of a multitude of macrolide antibiotics; 2) must specifically detect the microorganism; and 3) must be able to distinguish between a perfectly matched versus a mismatched sequence under in situ hybridization conditions. The specification has not adequately taught or provided sufficient guidance to obtain a representative number of such probes. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION:

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 53, 57-91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 53, and 57-85 are indefinite over the recitations of "microorganisms which are treated using macrolide antibiotics" because it is not clear as to how this recitation is intended to limit the claims. It is unclear as to whether this is considered to be a property of the microorganisms (e.g., that an individual infected with the microorganism can be treated with a macrolide antibiotic; that the microorganism is sensitive to the macrolide antibiotic) or if the claim is intended to include a step of treating the microorganism with the antibiotic. Furthermore, it is unclear as to what is intended to be meant by the phrase "wherein said microorganisms are usually treated using macrolide antibiotics." The claims do not set forth the conditions or circumstances for treatment with antibiotics and it is unclear as to what is meant by the fact that the microorganisms are **usually** treated with the antibiotic.

Claims 86-91 are indefinite over the recitation of "the sample" because this phrase lacks proper antecedent basis.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 53, 57-58, 60-85, 92, 93, and 101-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic (Antimicrobial Agents and Chemotherapy (Feb 1996) 40: 477-480) in view of Amann (Microbiological Reviews (March 1995) 59: 143-169) and Amann (Journal of Bacteriology (1990): 172: 762-770).

Versalovic teaches a method for detecting clarithromycin resistance to Helicobacter pylori. Versalovic teaches that an A to G mutation at position 2058 of the 23S rRNA of H. pylori confers resistance to the antibiotic clarithromycin. The reference teaches both the wild-type and mutant sequence of the 23S rRNA of H. pylori (see page 478). The reference also teaches that an A to a G mutation at position 2059 confers resistance to clarithromycin in H. pylori. The reference teaches that the mutations can be detected by sequencing the nucleic acids of H. pylori and by restriction enzyme analysis. However, the reference does not teach detecting the mutations by performing in situ hybridization.

Amann (1995) teaches methods for detecting the presence of a mutation in bacterial DNA. In the methods of Amann, intact microbial cells are contacted with a nucleic acid probe specific for a target rRNA sequence and subjected to hybridization (see, for example, pages 147-148 and 152-153). The in situ hybridization method of Amann allows one to effectively detect the presence of a single point mutation in the bacterial genome. Amann (for example, pages 156-157) also teaches using a mixture of probes so that multiple microorganisms can be detected simultaneously. Amann (page 158-166) addresses several criteria which may effect in situ hybridization efficiency and provides guidance as to how to improve the specificity and sensitivity of in situ hybridization. In particular, Amann acknowledges that some regions of the rRNA are less accessible for hybridization to probes due to the presence of secondary structures in the rRNA (see pages 159-160). Amann outlines the steps for evaluating the ability of a probe to effectively hybridize to the rRNA in situ and teaches how to optimize probes with respect to selecting an appropriately accessible target sequence, selecting optimal probes and hybridization conditions based on the probe's temperatures of dissociation. AT page 160, Amann states that "There is some indication (although from negative results) that certain regions might be inaccessible in certain phylogenetic groups. Sometimes, shifting the target site by just a few nucleotides has a major influence on the probe sensitivity." Amann (page 160) also teaches effective methods for labeling probes in order to enhance the sensitivity of in situ hybridization. Accordingly, Amann provides ample guidance as to how to effectively select and use a 23S rRNA probe for in situ hybridization and detection of a specific microorganism.

Additionally, Amann (1990) teaches in situ hybridization methods for detecting specific microorganisms. Amann teaches that in situ hybridization methods can be used to discriminate complementary from single-mismatched hybrids (see page 765).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Versalovic so as to have detected the 2058 mutation by whole-cell in situ hybridization in order to have provided a highly effective and rapid means for detecting clarithromycin resistance in H. pylori.

With respect to claims 66 and 67, Versalovic teaches obtaining the H. pylori from patient samples and growing H. pylori in a "presumptive medium" containing an indicator. With respect to claims 89, 90, 96 and 97, Versalovic teaches growing H. pylori in brain heart infusion agar containing fresh horse blood. It is a property of this media that it contains the reducing agent cysteine and a nitrogen source. With respect to claim 64, Versalovic does not teach analyzing the sample without culturing. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the H. pylori sample could be directly analyzed by hybridization without culturing because Amann teaches that the whole-cell in situ hybridization method is effective for detecting a single cell. One of ordinary skill in the art would have been motivated to have omitted the culturing step in order to have provided a more rapid means for detecting clarithromycin resistance in H. pylori. With respect to claims 68 and 69, Amann teaches fixing the cells prior to performing in situ hybridization. With respect to probes, Versalovic teaches a 19 bp region of 23S rRNA containing the 2058 mutation and Amann (1990) teaches the use of oligonucleotide probes of 15 to 25

nucleotides (page 763). Accordingly, it would have been obvious to one of ordinary skill in the art to have generated probes complementary to the regions set forth by Versalovic wherein said probes are 15-25 nucleotides in length in order to have provided probes useful for detecting the 2058 mutation. Probes complementary to the region set forth by Versalovic comprise at least 10 nucleotides of SEQ ID NO: 1. The sequence complementary to the region disclosed by Versalovic differs from present SEQ ID NO: 1 only in that it is missing a 3' T nucleotide. However, the sequence of the 23S rRNA of H. pylori was well known in the art at the time the invention was made. Given the teachings of Amann of generating probes of a length up to 25 nucleotides, it would have been obvious to one of ordinary skill in the art that additional probes could be generated which are of a longer length and which would comprise the full length sequence of SEQ ID NO: 1. In the absence of evidence of unexpected results, it would have been obvious to one of ordinary skill in the art to have generated additional probes of up to 25 nucleotides complementary to the region. Amann (1995 and 1990) also teaches using multiple probes simultaneously. Accordingly, it would have been further obvious to one of ordinary skill in the art at the time the invention was made to have included additional probes, including the wild-type probe, in order to have detected clarithromycin sensitivity in H. pylori or to detect other mutations in H. pylori.

Further, Amann (1995 and 1990) exemplifies the use of genus and species specific probes. It would have been further obvious to one of ordinary skill in the art to have included a genus or species specific probe in order to have confirmed the identity

of the organism. It is noted that Versalovic teaches examining H. pylori microscopically (page 477) and quantitatively detecting clarithromycin resistance (page 478).

5. **RESPONSE TO ARGUMENTS:**

In the response of September 26, 2003, Applicants state that Versalovic teaches detecting the 2058 mutation in Helicobacter using PCR, DNA sequencing or restriction enzyme analysis. It is asserted that Amann was not able to discriminate between the JG1 and LH1- subtypes of fibrobacter using in situ hybridization and had to rely on "state of the art technology" in place of in situ hybridization. Applicants thereby conclude that Versalovic and Amann teach away from using in situ hybridization to detect point mutations and that it is unexpected that one could detecting a single point mutation in mRNA by in situ hybridization. However, Versalovic and Amann do not in fact teach away from using in situ hybridization. The absence of a teaching of in situ hybridization in the Versalovic reference is not equivalent to a teaching that one should not employ in situ hybridization to detect point mutations. Additionally, Amann (1990) does in fact teach that one can use in situ hybridization to distinguish between perfectly matched and single-mismatched hybrids. Amann acknowledges that not all probes will be useful for detecting mismatches but that effective probes can be identified empirically. Amann (1995 and 1990) provides the guidance for selecting and developing probes that hybridize to rRNA and which can be used to discriminate between perfectly matched and mismatches hybrids.

Additionally, Applicants assert that the ability to detect a mismatch by in situ hybridization is unexpected. However, there is no basis in the specification as originally

filed for the proposed "unexpected results." While the specification (page 31) acknowledges that not all regions of the rRNA are available for in situ hybridization, the specification points to the teachings of Amann (1995; cited above) and Frischer (1996) as disclosing regions of the rRNA that are not accessible due to stable secondary structures or the binding of ribosomal proteins. The specification acknowledges, as does Amann (1995), testing is required to identify probes that can be used for in situ hybridization. The specification does not assert that it is unexpected that one could use a probe to detect mismatches in the rRNA and does not provide any guidance beyond the teachings of Amann for improving the method of in situ hybridization so as to allow for a more predictable means of detecting mismatches in rRNA. The "unexpected results" proposed by Applicants are not commensurate in scope with the teachings of the specification. The specification has taught only 4 probes that can be used to screen for Helicobacter clarithomycin resistance using in situ hybridization methods by detecting a single-nucleotide mutation in the 23S rRNA of Helicobacter, i.e., the probe ClaR1 which consists of SEQ ID NO: 1 and which detects the A2058G mutation, probe ClaR2 which consists of SEQ ID NO: 2 and which detects the A2059G mutation, probe ClaR3 which consists of SEQ ID NO: 3 and which detects the A2058C mutation, and the probe ClaWT which consists of SEQ ID NO: 4 and which detects wildtype Helicobacter. In view of the fact that Amann provides the guidance for performing in situ hybridization for the detection of point mutations, the ordinary artisan would have had a reasonable expectation of success of generating additional probes,

commensurate in scope with the presently claimed probes, which could be effectively used for in situ hybridization to detect point mutations in H. pylori.

6. Claims 86-90 and 94-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Amann (1995) and Amann (1990) in view of the Stratagene catalog.

The teachings of Versalovic and Amann (1995 and 1990) 7. are presented above. The combined references teach a method which requires the use of a 23S rRNA probe specific for the 2058 mutation of H. pylori, a presumptive medium, and an indicator substance for detecting antibiotic resistance. Versalovic does not teach packaging these reagents into a kit.

However, reagent kits for performing detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the reagents required to practice the method of Versalovic in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to detect antibiotic resistant strains of H. pylori.

7. Claims 91 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Amann (1995) and Amann (1990) the Stratagene catalog and further in view of Morotomi.

The teachings of Versalovic, Amann (1995 and 1990) and the Stratagene catalog are presented above. The combined references do not teach including urease in the kit.

Morotomi teaches that H. pylori may be detected using a urease indicator.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the urease indicator taught by Morotomi in the kit in order to have provided a kit that could be used to confirm the presence of H. pylori and could also be used to detect antibiotic resistant strains of H. pylori.

8. Claims 92, 93, 101 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Hiratsuka (GenBank Accession No. U27270, June 1995) and Gingeras (US Patent No. 6228575).

Versalovic teaches a method for detecting clarithromycin resistance to Helicobacter pylori. Versalovic teaches that an A to G mutation at position 2058 of the 23S rRNA of H. pylori confers resistance to the antibiotic clarithromycin. The reference teaches both the wild-type and mutant sequence of the 23S rRNA of H. pylori (see page 478). The reference also teaches that an A to a G mutation at position 2059 confers resistance to clarithromycin in H. pylori. The reference teaches that the mutations can be detected by sequencing the nucleic acids of H. pylori and by restriction enzyme

analysis. However, the reference does not teach detecting the mutations by performing hybridization and thereby does not teach probes to the 23S rRNA mutations.

It is noted that Versalovic (Figure 1) does teach the sequence of the wild-type 23S rRNA, as well s the sequence of the 2058 and 2059 mutations:

AGACGGAAAGACCCCGUGG – wildtype (clarithromycin sensitive)

AGACGG**G**AAGACCCCGUGG-- A2058G (clarithromycin resistant)

AGACGGA**G**AGACCCCGUGG – A2059G (clarithromycin resistant)

The A2058G sequence differs from the complement of SEQ ID NO: 1 only in that it is missing the 5' terminal nucleotide (i.e., the nucleotide complementary to the 3' terminal T in SEQ ID NO: 1). Additionally, the complete sequence of the 23S rRNA of Helicobacter pylori was known at the time the invention was made and is specifically taught by Hiratsuka (GenBank Accession No. U27270).

Allele specific oligonucleotides for detecting and distinguishing between target nucleic acids which differ by one nucleotide were well known in the art at the time the invention was made. Additionally, alternative methods employing hybridization probes for the detection of single-nucleotide mismatches were also well known in the art. In particular, Gingeras teaches probes for detecting a target nucleic acid wherein the probes are able to distinguish wildtype and mutant nucleic acids that differ by one nucleotide and teaches hybridization methods for using such probes (see, for example, columns 13 and 14). Gingeras teaches including species specific probes in the probe sets. Additionally, Gingeras teaches labeling of hybridization probes (column 8) and the use of probe sets containing individual probes that are fully complementary to or which

differ from the target nucleic acid by one nucleotide. The reference also exemplifies a number of allele specific probes which are of lengths from 15 to 20 nucleotides (see columns 24, 30 and 32). Gingeras (columns 20-21) teaches the use of the allele specific oligonucleotides to detect polymorphisms/mutations in rRNA regions that are associated with drug resistance.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have developed hybridization probes complementary to the "A2058G" sequence taught by Versalovic, wherein the probes comprised the sequence of SEQ ID NO: 1 or 10-30 mer fragments of SEQ ID NO: 1 because Gingeras teaches how to make hybridization probes complementary to nucleotide sequences that contain a single-nucleotide mutation/polymorphism and teaches the use of such probes for the purposes of distinguishing between wildtype nucleic acids and nucleic acids which differ from wildtype nucleic acids by a single nucleotide. One of ordinary skill in the art would have been motivated to have generated such probes in order to have facilitated the detection of clarithromycin resistant strains of H. pylori and to have allowed for the simultaneous analysis of multiple samples and the detection of multiple mutations in H. pylori samples.

9. Claims 86-90, 94-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Hiratsuka and Gingeras, as applied to claims 92-93 and 101-102 above, in view of the Stratagene Catalog.

The teachings of Versalovic, Hiratsuka and Gingeras are presented above. Additionally, Versalovic teaches obtaining the H. pylori from patient samples and

growing H. pylori in a "presumptive medium" containing an indicator. Versalovic teaches growing H. pylori in brain heart infusion agar containing fresh horse blood. It is a property of this media that it contains the reducing agent cysteine and a nitrogen source.

Accordingly, the combined teachings references teach a method for detecting H. pylori which requires the use of a 23S rRNA probe specific for the 2058 mutation of H. pylori, species specific probes, a presumptive medium, and an indicator substance for detecting antibiotic resistance. The combined references do not teach packaging these reagents into a kit.

However, reagent kits for performing detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the reagents required to practice the method of isolating H. pylori and detecting H. pylori by hybridization in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to detect antibiotic resistant strains of H. pylori.

As stated in the MPEP 2111.03 which states "On the other hand, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a

process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone". In the present case, the recitation in the claims of a kit "for determining macrolide antibiotic resistance in microorganisms by in-situ hybridization," does not carry weight with respect to the obviousness of the kit and does not distinguish the claimed kit over the kits suggested by the prior art disclosures.

10. . Claims 91 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Versalovic in view of Hiratsuka, Gingeras and the Stratagene Catalog, as applied to claims 86-90 and 94-97 above, and further in view of Morotomi.

The teachings of Versalovic, Hiratsuka, Gingeras and the Stratagene Catalog are presented above. The combined references do not teach including urease in the kit.

Morotomi teaches that H. pylori may be detected using a urease indicator.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included the urease indicator taught by Morotomi in the kit in order to have provided a kit that could be used to confirm the presence of H. pylori and could also be used to detect antibiotic resistant strains of H. pylori.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
November 4, 2003

CARLA J. MYERS
PRIMARY EXAMINER